A forum about CNS energy metabolism.

To participate in this forum, send communications to ***rwalbers@helix.nih.gov*.**

"The combination of a cerebral respiratory quotient of unity, an almost stoichiometric relationship between oxygen uptake and glucose consumption, and the absence of any significant arteriovenous difference for any other energy-rich substrate is strong evidence that the brain normally derives its energy from the oxidation of glucose." [BN5ch31p660, BN6ch31p657]

"Clearly, the functions of nervous tissues are mainly excitation and conduction, and these are reflected in the unceasing electrical activity of the brain. The electrical energy is ultimately derived from chemical processes, and it is likely that most of the brain's energy consumption is used for active transport of ions to sustain and restore the membrane potentials discharged during the process of excitation and conduction (see Chap. 3)." [BN5ch31p661]

"A major fraction of cerebral energy production is required for extrusion of intracellular Na^+ that enters during excitation and secondary transport. Cation flux during action potentials is two to three orders of magnitude greater than in the resting state." [B6ch5p99]

How is metabolism coupled to function in the central nervous system?

The conventional view:

"Significant control probably resides at several levels: blood flow, metabolite flux at cell membranes, as well as regulation of intracellular metabolic rates. Brain arteries receive extensive sympathetic inervation.... Cerebral microvasculature may be regulated ....

"...The major postulated metabolic control mehanisms, through phosphofuctokinase and through the supply of ADP to mitochondria, are in turn functions of energy utilization.

"Thus to a large extent CMRs may respond passively to neural activity at the cell level. It may be that neural mechanisms can also "anticipate" functional central nervous system requirements ....various experimentally imposed stresses [hypoxia for example] produce changes in cyclic nucleotides and other factors that may link central nervous system metabolism to extrinsic neural control (Magistretti et al 1981)."

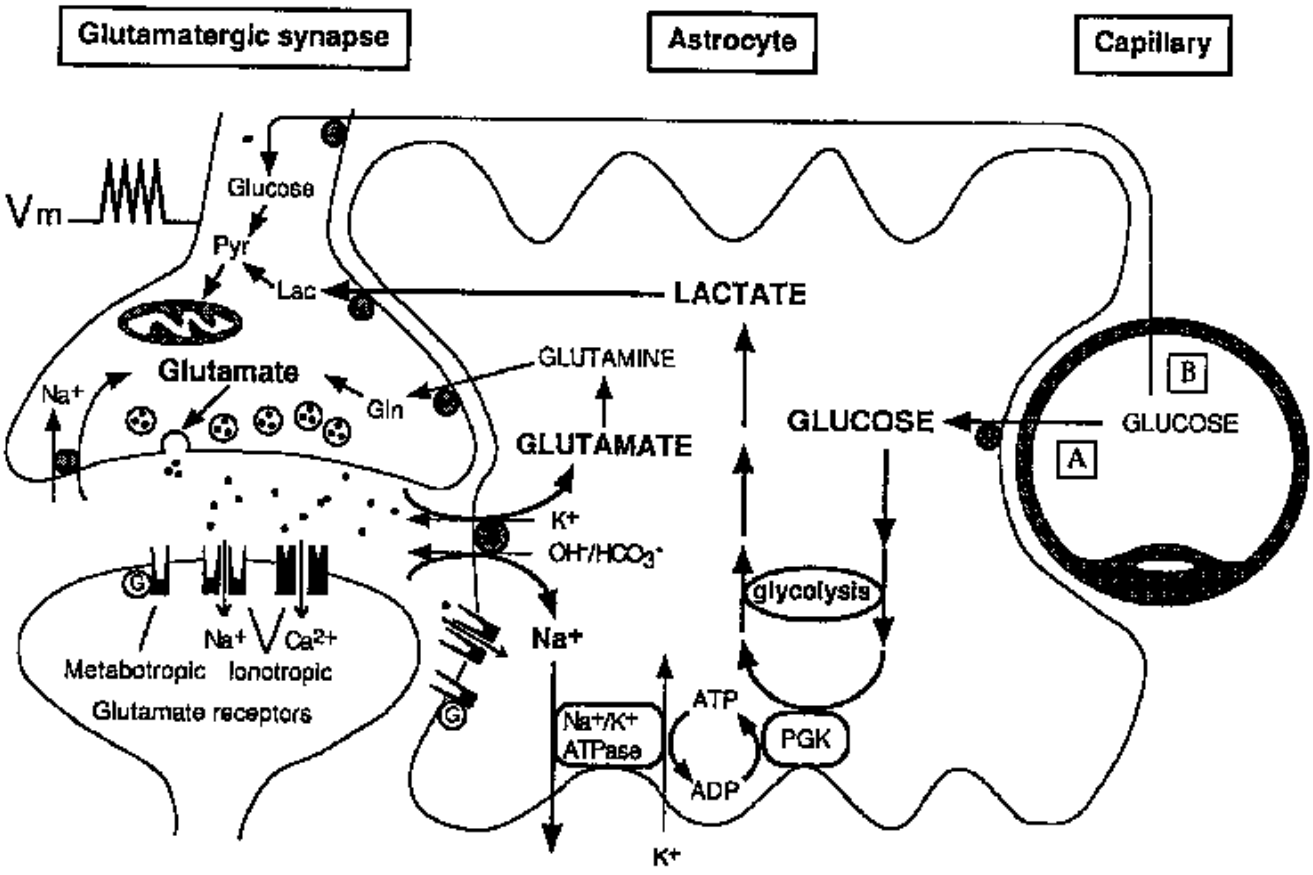
[from Albers (1985) p189 in Developmental Neurochemistry, ed. Wiggins et al, U Tex Press]

A different view:

Magistretti and coworkers have proposed two hypotheses which require that **astrocytes play an essential role in neuronal energy metabolism** [1996, J Neurosci 16:877; 1994, PNAS 91:10625 ; 1999, Science 283:496]:

I. Aerobic glycolysis in the CNS involves interactions between neurons and astrocytes:

Hypothesis: **the physiological coupling of brain metabolism to neural activity consists principally of glutamate-induced glycolysis in astrocytes.**



From Tsacopoulos and Magistretti, 1996, J. Neuroscience 16:877-885.

- The entrance of glucose into the central nervous system from the capillaries occurs primarily into astrocytes.
- Astrocytes metabolize glucose to lactate and secrete lactate.
- Neurons take up lactate as a primary substrate for oxidative metabolism.

II. Neuronal activity regulates the rate of aerobic glycolysis by a mechanism involving glutamate release from neurons and glutamate uptake into astrocytes.

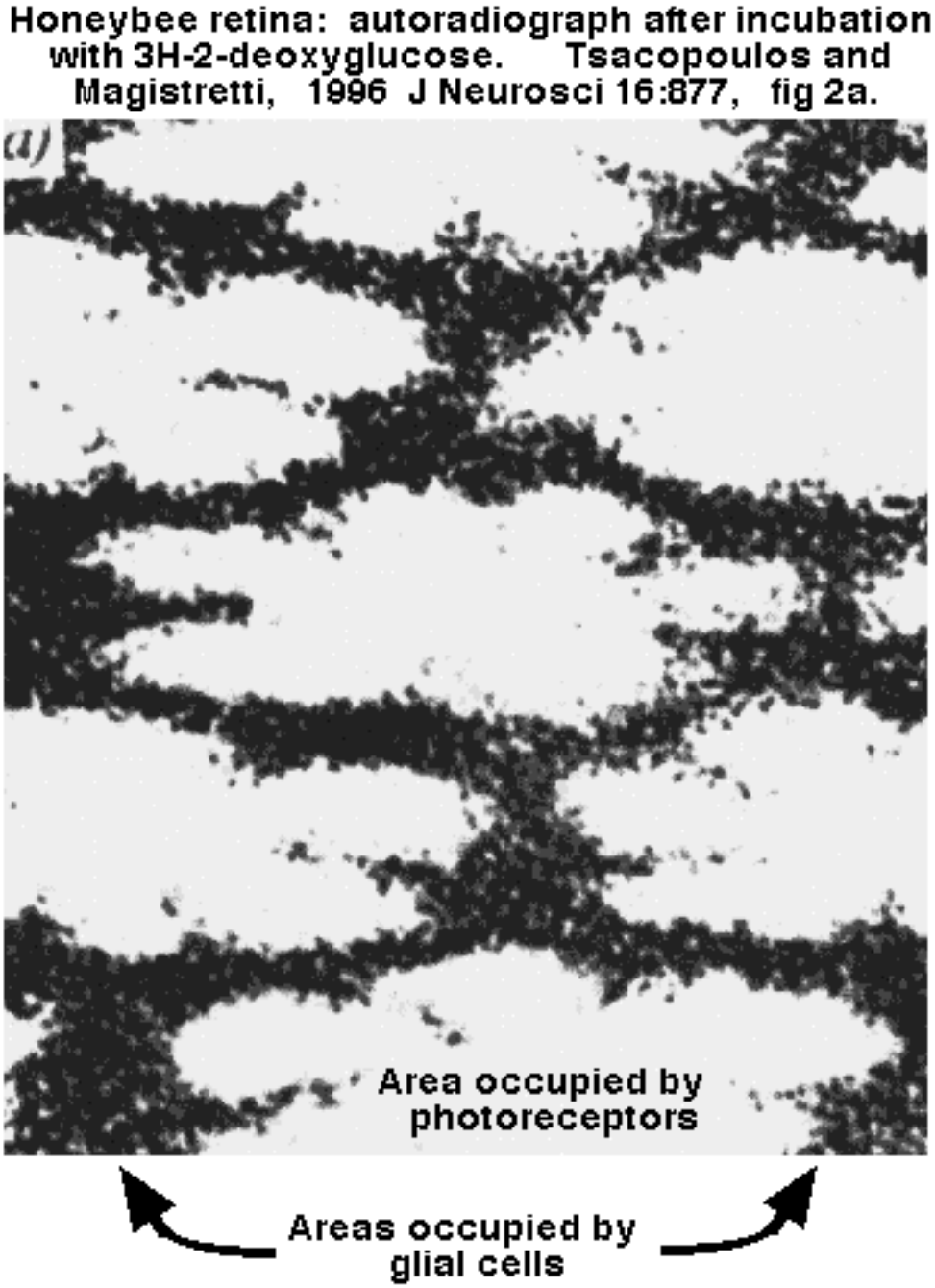
- Glutamate is the primary neurotransmitter released by excitatory synapses in the CNS. [BN6ch15p316]
- Glutamate is taken up by astrocytes by a Na^+ cotransporter [BN6ch15fig. 7].
- Na+ influx into astrocytes stimulates the astrocytic sodium pump which produces ADP.
- Increased levels of astrocytic ADP will stimulate glycolysis and lactate transport into neurons.
- Lactate uptake by neurons will stimulate neuronal oxidative ATP production.

Supporting data:

1. **If astrocytes play an essential role in neuronal energy metabolism**:

- a) **Uptake of 2-deoxyglucose should be primarily into astrocytes**:

  Data : *Honey bee retina:*their beautifully regular interposition of photoreceptors in matrix of glial cells allows elegant demonstration of differential deoxyglucose uptake in this case.



- b) **Lactate should be released by astrocytes as a result of neuronal activity.**

  Data :

- c) **Lactate, rather than glucose, should be the primary *in vivo*** substrate of neurons.

  Data :

2. **If reuptake of neurotransmitters into astrocytes play an essential role in regulating neuronal energy metabolism:**

- a) **Reuptake of some neurotransmitters (including glutamate and perhaps GABA) should**

occur primarily into astrocytes via Na^+-dependent cotransporters.

Data 1: The L-glutamate/ L-aspartate transporter GLT-1 is distributed in astrocytes throughout the brain and spinal cord.[Rothstein JD ; Martin L ; Levey AI et al, Neuron 1994 Sep;13:713-25]

Data 2: Uptake of exogenous [^{3}H]glutamate [is] localized specifically in Muller cells and pigment epithelium. [Ehinger and Falck: , 1971 Brain Res 33:157-172].

Data 3: The L-glutamate/L-aspartate transporter (GLAST) is present in Muller cells. Derouiche A ; Rauen T 1994, Hippocampus:4:297-306

- b) **The influx of Na^+ into astrocytes accompanying neurotransmitter reuptake should be sufficient to account for the observed stimulation of glycolysis.**

  Data: NMR spectroscopy measurements of the rate of cerebral glutamine synthesis from ^{13}C-glucose in rats was interpreted to indicate a rate of 0.21 micromole/(gram-min) [Sibson et al. 1997. Proc. Nat. Acad. Sci. 94:2699] In a subsequent study, they employed the same type of measurements in rats under different levels of anesthesia. They conclude that the *increment* in cerebral glucose oxidation that is attributable to electrical activity is approximately equal to the rate of conversion of glutamate to glutamine. [Sibson et al. 1998. Proc. Nat. Acad. Sci. 95:316]

- c) **Increase in astrocytic intracellular Na^+ should activate the sodium pump;**

  Data: Addition of a synthetic Na^+ ionophor to pure cultures of astrocytes more than doubles the rate of tracer deoxyglucose phosphorylation; this stimulation is partially suppressed by the sodium pump inhibitor, ouabain. [Takahashi, Driscoll, Law and Sokoloff, 1995, PNAS 92:4616]

- d) **Intracellular turnover of astrocytic ATP should increase in response to neuronal activity**

  Data :

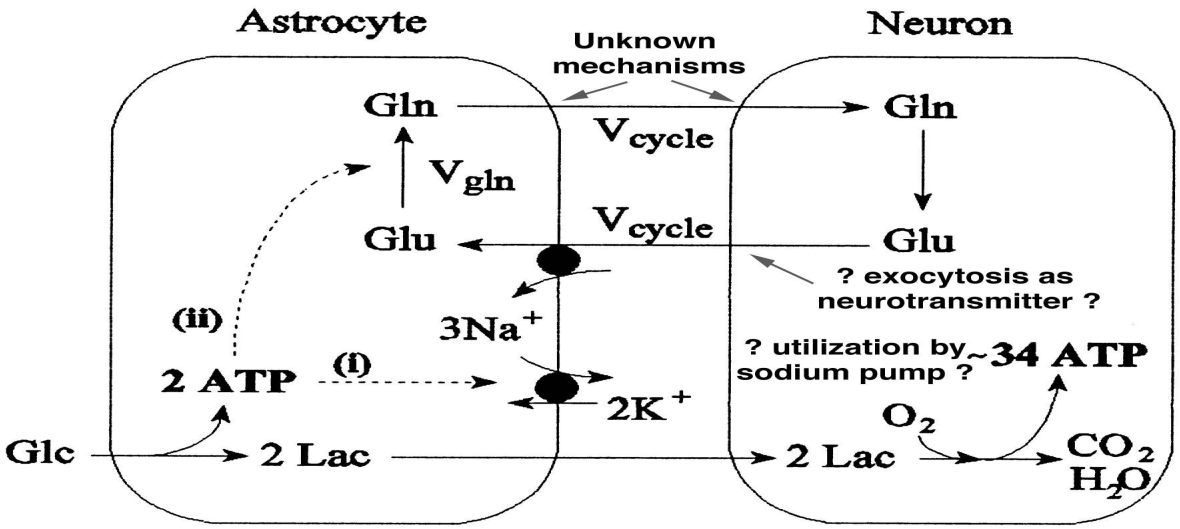
- e) **Astrocytic glycolysis should be stimulated by neuronal activity.**

  Data :

- f) **Astrocytic lactate efflux should be taken up by neurons and stimulate neuronal oxidative metabolism.**

  Data: A cDNA clone which encodes a monocarboxylate transporter (ratMCT1) was isolated from a rat small intestinal cDNA library..... RNA transcripts hybridizing to ratMCT1 cDNA were detected in rat brain, [Takanaga H ; Tamai I ; Inaba S et al, 1995 ; Biochem Biophys Res Commun 217:370-7]

"The two molecules of ATP required ... to take up glutamate and convert it to Gln can be exactly balanced by the two ... ATP produced through glycolysis of one Glc ....."



Modified from fig. 4 of Sibson et al, 1998, Proc Nat Acad Sci 95:316-321

The above figure is from fig. 4 of Sibson et al PNAS 95:316 (1998) with added comments referring to unknown mechanisms.

Complications, elaborations and ramifications:

A reasonable and widely accepted hypothesis has been that the energy requirement for nerve activity is primarily the requirement to maintain the ion gradients and that " the passage of finite current of Na^+ into the cell ..... can be expected to stimulate Na,K-ATPase activity to restore the ionic gradients to normal, and such ATPase activity would, in turn, stimulate energy metabolism." (Basic Neurochemistry. chapter 31. Circulation and Energy Metabolism of the Brain by Donald D. Clarke and Louis Sokoloff)

Here are some questions for further discussion:

- What would be the functional advantage of the proposed more complex process requiring astrocytes to feed lactate to neurons?
- Can the proposed glutamate regulatory process work? Glutamate and GABA transporters appear to be driven primarily by Na^+ cotransport with a fixed stoichiometry of probably not more than 2 Na^+ per neurotransmitter molecule. How much neurotransmitter is released relative to the observed amount of metabolic stimulation?
- If necessary, is there an amplification mechanism that could make this hypothesis work?

A century-old hypothesis is that glia have a role in neuronal nutrition. This was originally based on their strategic spatial interposition between capillaries and neurons. In addition it has long been known that brain glycogen is localized in astrocytes and that trauma such as a stab wound will lead to depletion of astrocytic glycogen in surrounding brain tissue.